Journal of the American College of Cardiology Vol. 48, No. 2, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.04.031

EDITORIAL COMMENT

Prevalence of Soft Plaque Detection With Computed Tomography*

Matthew J. Budoff, MD, FACC
Torrance, California

Coronary calcium assessment is being increasingly used in clinical practice for risk stratification. Higher coronary calcium scores are associated with increased plaque burden and increased cardiovascular risk. One concern is the presence of isolated lipid-laden (soft) plaque in the setting of a negative study (zero calcium score). In this issue of the *Journal*, Hausleiter et al. (1) suggest that the ability to detect lipid-laden coronary plaques with cardiac computed tomography (CT) angiography would possibly improve risk stratification of these patients. The authors studied 161 consecutive patients with an intermediate risk for having coronary artery disease (CAD) and CT datasets were evaluated for the presence of coronary calcifications, noncalcified plaques, and/or lumen narrowings. Coronary calcifications were absent in 63 of 161 (39%) patients, and the overall prevalence of patients with noncalcified plaques as the only manifestation of CAD was 6.2% (10 of 161 patients). The authors surmise that with CT, "discernible noncalcified atherosclerotic coronary plaques can be detected in a large group of patients with an intermediate risk for having CAD. The assessment of these plaques by CT angiography may allow for improved cardiovascular risk stratification." The basic premise of the paper is that the detection of isolated soft plaque adds significant information for the clinician. Thus, the question becomes: does noncalcific plaque detection improve on coronary calcium assessment?

See page 312

Several prospective studies have been conducted evaluating the negative predictive power of coronary artery calcification (CAC) for obstructive disease. As a cost-effective diagnostic test, noncalcific plaque detection would have to identify a significant number of patients with obstructive disease in the absence of CAC. A large study, evaluating consecutive symptomatic persons undergoing cardiac catheterization, defined the frequency of noncalcific lesions causing obstruction. Knez et al. (2) studied 2,115 consecutive symptomatic patients (n = 1,404 men; mean age, 62 ± 19 years) with no previous diagnosis of CAD, finding CAC in more than 99% of patients with obstructive CAD. No calcium was found in 7 of 872 men (0.7%) and in 1 of 383 women (0.02%) who had significant luminal stenosis on coronary angiography. Seven of these 8 patients were younger than 45 years of age. Assuming perfect sensitivity, noncalcific plaque detection by CT would only have identified 8 additional patients of 1,255 (0.6%). Clearly, evaluating patients with a probability of disease of only 0.6% would lead to many more false-positive than true-positive results, and the cost and risks could not be justified. Another large CAC and angiography study suggests the sensitivity of CAC for obstruction was 96% (3). Thus, 4% of symptomatic patients with obstructive disease were not detected by use of CAC testing. Assuming noncalcific plaque detection with CT has a 78% sensitivity and 90% specificity (4), this test will identify 3 cases per 100 to be true-positive and 9 to be false-positive, for a positive predictive value of only 25%. Subjecting patients to cardiac catheterization with such a low pretest probability and positive predictive value is not warranted.

However, focusing this application where calcification scoring is less accurate (younger patients, patients with smoking history) may prove clinically useful. There are several studies demonstrating that CAC measurement has a lower sensitivity in patients younger than 40 or 45 years of age (2,3). The most practical application of CT angiography is improving on the limited specificity of CAC for obstructive disease. Because the presence of CAC often is associated with nonobstructive disease, specificity for obstructive disease is reduced. The determination of significant stenotic disease in persons with some level of calcification will undoubtedly be useful to the clinician and patient.

The use of contrast CT for risk stratification of the asymptomatic patient is problematic. The need for risk stratification is the greatest for the person at intermediate risk of cardiac events (5). Persons without coronary calcium (scores of zero) are at low risk of both obstructive disease and future cardiovascular events, so further risk stratification is generally not warranted. Large prospective trials demonstrate the risk of cardiac events in patients with patients without coronary calcification (scores of zero) to be 0.1% per year. One recent study of 924 symptomatic patients undergoing cardiac catheterization and CAC measurement demonstrated no cardiac events over the next 3 years in patients with scores of zero, whereas 50 myocardial infarctions occurred in those with calcification. In asymptomatic patients, studies demonstrate that a positive test is associated with an approximate 10- to 12-fold increased risk of cardiac events (6,7). In one large prospective, population-based study, 4,903 asymptomatic persons ages 50 to 70 years underwent electron beam CT scanning of the coronary arteries. At 4.3 years, 119 patients had sustained at least one cardiovascular event. For coronary calcium score threshold >100 versus <100, relative risk was 9.6 for all cardiovas-

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From Division of Cardiology, Los Angeles Biomedical Research Center at Harbor-UCLA, Torrance, California. Dr. Budoff is on the Speakers Bureau for General Electric.

cular events, 11.1 for all CAD events, and 9.2 for nonfatal myocardial infarction and death. The coronary calcium score predicted CAD events independently of standard risk factors and C-reactive protein ($p = 0.004$) and was superior to the Framingham risk index in the prediction of events (area under the receiver-operating characteristic curve of 0.79 ± 0.03 vs. 0.69 ± 0.03, $p = 0.0006$). More importantly, only 8 of 1,504 (0.5%) persons with scores of zero had a coronary event during the next 4.3 years, and the annual event rate was only 0.1%, which makes patients without coronary calcification very low risk, diminishing the need for further risk stratification with such tests as cardiac CT angiography. Isolated lipid-laden plaque is only one potential cause of cardiac events in this population. These patients could have suffered events from a nonatherosclerotic cause (thrombus, spasm, embolism), had nondetectable plaque present (the sensitivity of lipid-laden plaque by CT compared with intravascular ultrasound is only 78%) (4), or had another risk for CAD (inflammation, advanced lipid abnormalities, endothelial dysfunction, or one of the myriad of new cardiovascular risk factors being suggested). To significantly change management, CT angiography would have to increase a person's risk by 20-fold to rise from 0.1% per year to >2.0% per year (low risk to high risk for cardiovascular events). A younger asymptomatic population poses an even greater challenge to improve upon coronary calcium risk stratification with CT angiography. Taylor et al. (7) prospectively followed 3,000 persons (mean age, 43 years) for 3 years. The CHD events occurred in only 2 of 1,263 participants without CAC (event rate 0.16%; $p < 0.0001$). Thus, a negative scan was associated with a 0.05% per year risk. In this cohort, findings on CT angiography would have to afford a 40-fold risk to move patients to the high-risk category.

The identification of a noncalcified plaque may very well be a plaque at an earlier stage of atherosclerosis, more amenable to antiatherosclerotic therapies. Identifying a person with a large area of lipid-laden plaque and then initiating lipid-lowering therapy to treat the asymptomatic CAD has logical appeal. However, one question is whether CT angiography can properly differentiate different types of noncalcific atherosclerotic plaque. Fibrous plaque generally is considered more stable (less vulnerable), whereas soft plaques with a large lipid core are far more vulnerable to rupture. Several CT studies have demonstrated that the lipid-rich plaque has a lower, but overlapping attenuation pattern to fibrous-rich plaque (4). The mean CT density values for lipid-laden plaques are usually around 30 to 50 Hounsfield units (HU) whereas the attenuation of a more fibrous lesion is around 90 HU. Although there is no issue about detecting noncalcific plaque from the blood pool or calcium, there is substantial overlap between lipid-laden and fibrous plaque, not always permitting consistent differentiation (4). Before clinical use of CT angiography for soft plaque detection, further studies are needed to demonstrate inter-reader and interscan reproducibility of the measure, autopsy studies are needed to validate quantification and identification of plaque burden, and validation of CT modalities ability is needed to separate coronary plaque composition into lipid- or fibrous-rich plaques.

For the asymptomatic person, it appears that coronary calcium detection is better suited to identify the vulnerable patient (that person who is at significantly increased risk of future cardiovascular events). The measurement of CAC requires no contrast, minimal radiation exposure, and takes only minutes to perform. A vulnerable plaque is defined by a thin fibrous cap (measured in microns, below the resolution of CT), associated with inflammatory cells and a lipid-laden core. Whether CT angiography can accurately depict the lipid-laden core needs more research. The authors (1) correctly conclude that "the risk for ischemic events in patients with noncalcified plaques as well as the additive value of noncalcified plaque detection over traditional calcium scoring are currently not known." The accuracy in the evaluation of soft plaque is improving with technological advancements with CT, and we are coming closer to defining the vulnerable plaque in a noninvasive manner. It would not be surprising to find that current information from CT angiography significantly influences cardiac morbidity or mortality. We may also come to rely on this modality to monitor plaque stabilization and potential regression in patients receiving antiatherosclerotic therapy.

The use of CT angiography is currently well suited for the symptomatic patient, potentially identifying those patients who need revascularization and/or advanced medical therapy. The use of CT angiography remains a robust method to evaluate coronary stenosis and will assist clinicians in evaluating congenital heart disease, coronary anomalies, pre-electrophysiology procedures, diagnosis of obstructive CAD in the symptomatic person and evaluation postrevascularization. The implications of isolated noncalcific plaque are currently unknown, and making assumptions about vulnerability may be premature. Current data strongly suggests a person with a negative calcium score is at very low risk for cardiovascular events and obstructive disease (8). The use of CT angiography in this setting to try to modify risk will require significant research before clinical use.

Reprint requests and correspondence: Dr. Matthew J. Budoff, Los Angeles Biomedical Research Center at Harbor-UCLA, 1124 West Carson Street, RB2, Torrance, California 90502. E-mail: mbudoff@labiomed.org.

REFERENCES

1. Hausleiter J, Meyer T, Hadamitzky M, Kastrati A, Martinoff S, Schömig A. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. J Am Coll Cardiol 2006;48:312–8.
2. Knez A, Becker A, Leber A, et al. Relation of coronary calcium scores by electron beam tomography to obstructive disease in 2,115 symptomatic patients. Am J Cardiol 2004;93:1150–2.
3. Budoff MJ, Raggi P, Berman D, et al. Continuous probabilistic prediction of angiographically significant coronary artery disease using electron beam tomography. Circulation 2002;105:1791–6.

4. Leber AW, Knez A, Becker A, et al. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. J Am Coll Cardiol 2004;43: 1241–7.
5. Greenland P, Smith SC, Grundy SM, et al. Improving coronary heart disease risk assessment asymptomatic people. Role of traditional risk factors and noninvasive cardiovascular tests. Circulation 2001;104: 1863–7.
6. Arad Y, Roth M, Newstein D, et al. Coronary calcification, coronary risk factors, and atherosclerotic cardiovascular disease events. The St. Francis Heart Study. J Am Coll Cardiol 2005;46:158–65.
7. Taylor AJ, Bindeman J, Feuerstein I, et al. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors. J Am Coll Cardiol 2005;46:807–14.
8. LaMonte MJ, FitzGerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol 2005;162:421–9.